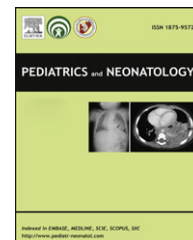


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CASE REPORT

A Novel Mitochondrial DNA 8597T > C Mutation of Leigh Syndrome: Report of One Case

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Leigh syndrome is an early-onset progressive neurodegenerative disorder with a characteristic neuropathology consisting of focal, bilateral lesions in one or more areas of the central nervous system. The brain images of Leigh syndrome are characterized by markedly symmetrical involvement, most frequently of the putamen. We report a 2-year-old girl with Leigh syndrome manifested as acute onset of altered level of consciousness. Brain magnetic resonance images showed abnormal signal intensity over the bilateral basal ganglia and cerebellar dentate nuclei. Despite normal biochemical studies, in particular serum lactate levels, magnetic resonance spectroscopy demonstrated a downward doublet lactate peak. The diagnosis of Leigh syndrome was subsequently confirmed by genetic study which showed a novel mutation at 8597T>C of the mitochondrial *ATPase6* gene.

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1. Introduction

Leigh syndrome (LS) is an inherited neurodegenerative disease that presents itself as a rapidly progressive phenotype and usually emerges in infancy and childhood.

Clinical presentations may vary, include change level of consciousness, brain stem and cerebellar dysfunction that result in stuporous, floppiness, hypertonicity and apneustic respiration.¹ Laboratory findings may show metabolic acidosis with elevated lactate level in the brain or cerebrospinal fluid (CSF).^{2,3}

Magnetic resonance (MR) images in LS are characterized by symmetrical T2 prolongation of the basal ganglia and brainstem.^{2,3} MR spectroscopy in patients with LS may reveal elevated lactate peak in the basal ganglia region,

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which can help in detecting neurometabolic disease including mitochondrial disease.⁴

Leigh syndrome is generally attributed to mutations in mitochondrial or nuclear encoded genes. The most frequently mutated mitochondrial gene is *ATPase 6*, which encodes for a subunit of respiratory chain complex V.⁵ We present a 2-year-old girl with this disorder bearing a novel mutation in the mitochondrial *ATPase 6* gene.

2. Case Report

A 2-year-old girl was the first child of nonconsanguineous parents. She had normal birth history, and her developmental was normal. At the age of 2 years old, she had pyretic illness, with subsequent unstable gait for 2 days, altered level of consciousness, respiratory failure and external ophthalmoplegia. Her laboratory tests, including white blood cell counts, C-reactive protein, electrolytes, ammonia, blood gas, blood lactate and cerebrospinal fluid examination were normal. Muscle biopsy with histochemistry stains showed a normal result. Glucose lactate stimulation test was normal. Assays of urinary organic acids and blood amino acids were within normal limits. Brain MR imaging showed symmetric abnormal signal intensity over the bilateral lentiform nuclei, caudate nuclei, posterior parts of the thalami, substantia nigra of the midbrain, posterior surface of the medulla oblongata, and cerebellar dentate nuclei (Figure 1). Proton MR spectroscopy demonstrated a downward doublet lactate peak (Figure 2). Subsequently, molecular genetic analysis via sequencing of the mitochondrial *ATPase6* gene was

performed. Written informed consent was obtained from the patient's parents. Total DNA was extracted from white blood cells and skeletal muscle by using the Puregene DNA purification kit (Qiagen, Valencia, CA, USA). The mitochondrial DNA, including mitochondrial *ATPase6*, was amplified by polymerase chain reaction (PCR). Point mutations were searched for the mitochondrial *ATPase6* gene by direct sequencing of the purified PCR products. Sequence analysis of the mitochondrial *ATPase6* gene in the patient revealed a novel heteroplasmic T → C substitution at mt 8597(8597T>C) in mitochondrial *ATPase6* gene (Figure 3). The mutation results in the substitution of a highly conserved isoleucine to threonine at codon 24. The proportions of the mutation in the patient's blood and muscle specimens were greater than 95%.

After being diagnosed as a case of LS, the patient was administrated with coenzyme-Q (30 mg/day). Thirty days later, the patient presented with stupor, feeding difficulty and hypertonicity of four limbs. EEG showed generalized slowing activities, prolonged latency of auditory evoked potentials was found. The follow-up MR images on admission Day 30 revealed brain atrophy with encephalomalacia and hemorrhagic necrosis (Figure 4). At the age of 3 years old, she had mental regression, feeding difficulty and spastic quadriplegia.

3. Discussion

Leigh syndrome, characterized by symmetrical necrosis in the brain stem, basal ganglia and thalamus in infancy or

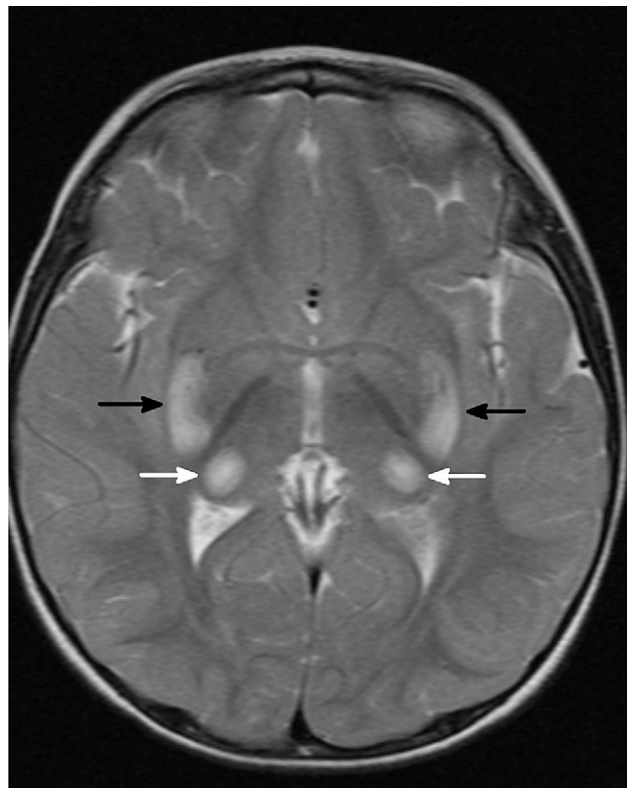


Figure 1 Axial brain MRI shows symmetrical high signal intensities in the putamen (black arrows) and posterior parts of thalami (white arrows). MRI = magnetic resonance imaging.

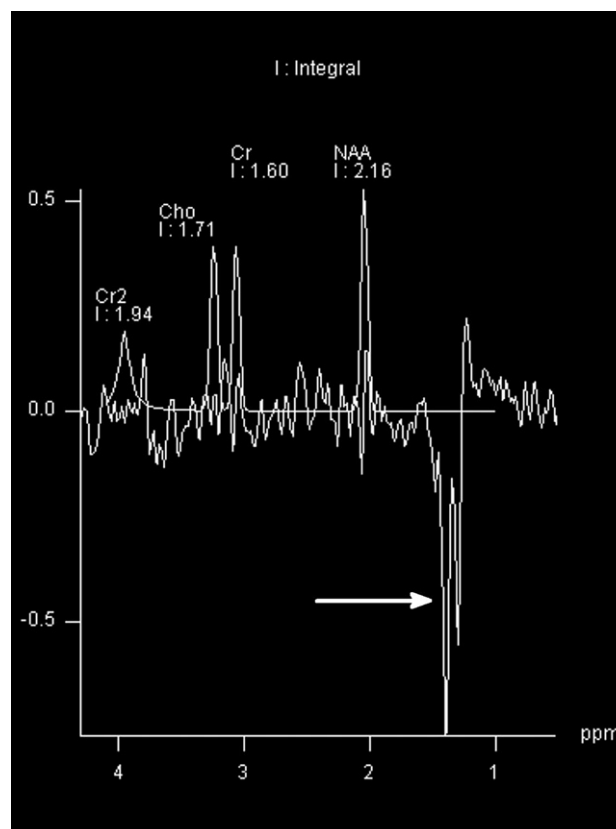


Figure 2 MR spectroscopy shows a downward doublet, the lactate peak over the putamen (arrow). MR = magnetic resonance.

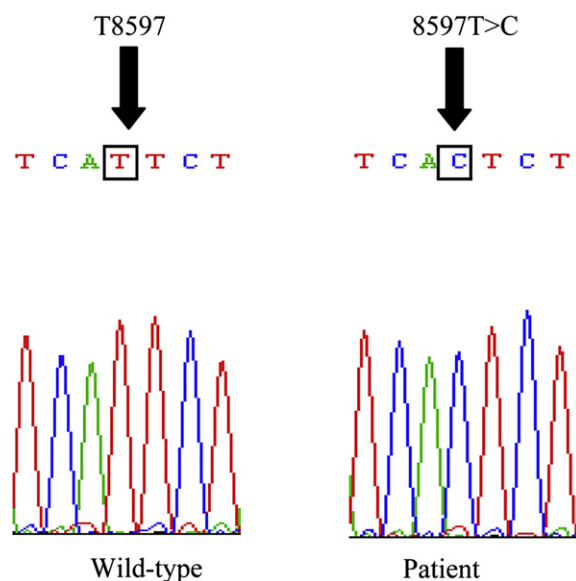


Figure 3 Sequence analysis of mitochondrial *ATPase6* gene in the patient shows a mutation 8597T>C.

childhood, results from heterogeneous biochemical abnormalities in mitochondria.⁶ Although elevated lactate in plasma or CSF is commonly seen in the patients with mitochondrial diseases,⁷ the sensitivity of lactic acidemia for the diagnosis of LS remains varied.^{2,3,5,6} Because most

other nonmitochondrial diseases that involve the basal ganglia lack lactate doublet, spectroscopy may be useful for diagnosing LS.⁸ In this case, though, the results of the initial blood lactate level, analysis of blood gas, and glucose lactate stimulation test were all normal. The brain magnetic imaging studies showed abnormal signal intensities over the basal ganglia; in addition, brain MR spectroscopy also demonstrated elevated lactate peak at the onset of the disease. Therefore, these findings in our case are compatible with clinical manifestations of LS.

LS was reported to be mutated in mitochondrial or nuclear coded genes. Mutation of mitochondrial genes to manifest clinically requires a certain heteroplasmy rate.⁹ The most frequently mutated mitochondrial gene in LS is *ATPase6* gene, which encodes in the subunit of respiratory chain complex V. The most frequently reported mitochondrial *ATPase6* genes were transversion 8993T>C and 8993T>G. A less common mutation in *ATPase6* gene is 9176T>C, which was initially described in two familial siblings with bilateral striatal necrosis but a relatively nonprogress course.⁵ In contrast to the milder phenotype, Dionisi-Vici et al¹⁰ reported a more fulminant clinical course in a family with two siblings, who presented as sudden unexpected death in infancy. Their symptoms developed during the first years of life without specific signs. Symmetrical spongiform of the brain, mainly affecting the basal ganglia and brain stem, and subsequent poor prognosis were noticed; these features resemble those of our case.

In conclusion, the finding of the novel mutation at mt8597T>C may expand the spectrum of mutation in mitochondrial genes with subsequent LS. MR spectroscopy of the brain may be helpful in diagnosis of LS without lacticemia.

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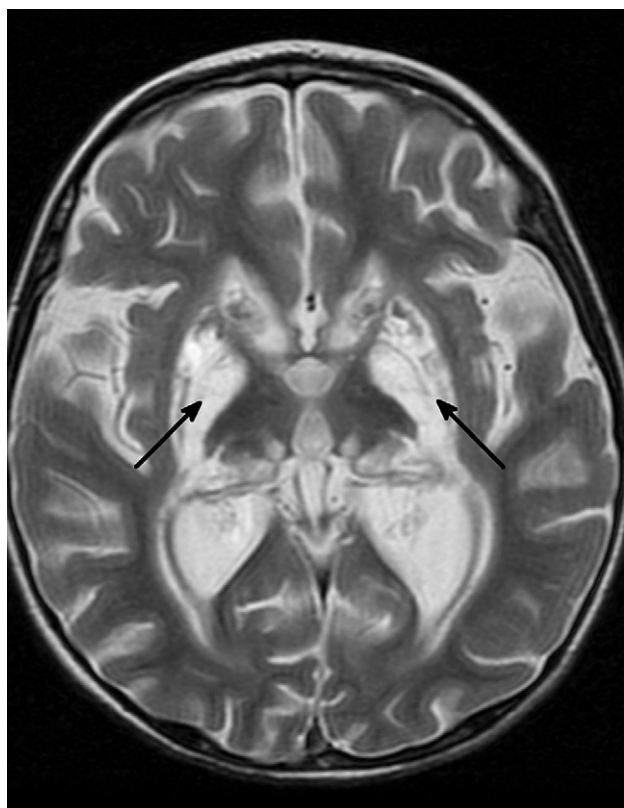


Figure 4 Axial brain MRI shows generalized brain atrophy and abnormal signal intensities over the bilateral lentiform nuclei and white matter of the parieto-occipital regions, with cystic change and high signal intensities (arrows). MRI = magnetic resonance imaging.